HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EPIDIOLEX® safely and effectively. See full prescribing information for EPIDIOLEX.

EPIDIOLEX® (cannabidiol) oral solution
Initial U.S. Approval: 2018

----------RECENT MAJOR CHANGES ----------
Dosage and Administration (2.4) 02/2022

----------INDICATIONS AND USAGE----------
EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older (1)

----------DOSAGE AND ADMINISTRATION----------
- Obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment. (2.1, 5.1)
- See Full Prescribing Information for titration. (2.2, 2.3)

Seizures Associated with Lennox-Gastaut Syndrome or Dravet Syndrome
- The recommended starting dosage is 2.5 mg/kg by mouth twice daily (5 mg/kg/day). After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day). (2.2)
- Based on individual clinical response and tolerability, EPIDIOLEX can be increased up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day).

Seizures Associated with Tuberous Sclerosis Complex
- The recommended starting dosage is 2.5 mg/kg by mouth twice daily (5 mg/kg/day). Increase the dose weekly by 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated, to a recommended maintenance dosage of 12.5 mg/kg twice daily (25 mg/kg/day). (2.3)

Patients with Impaired Hepatic Function
- Dosage adjustment is recommended for patients with moderate or severe hepatic impairment. (2.6, 8.6)

----------DOSAGE FORMS AND STRENGTHS----------
Oral solution: 100 mg/mL (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to cannabidiol or any of the ingredients in EPIDIOLEX (4)

----------WARNINGS AND PRECAUTIONS----------
- Hepatocellular Injury: EPIDIOLEX can cause transaminase elevations. Concomitant use of valproate and higher doses of EPIDIOLEX increase the risk of transaminase elevations. See Full Prescribing Information for serum transaminase and bilirubin monitoring recommendations. (5.1)
- Somnolence and Sedation: Monitor for somnolence and sedation and advise patients not to drive or operate machinery until they have gained sufficient experience on EPIDIOLEX. (5.2)
- Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts. (5.3)
- Hypersensitivity Reactions: Advise patients to seek immediate medical care. Discontinue and do not restart EPIDIOLEX if hypersensitivity occurs. (5.4)
- Withdrawal of Antiepileptic Drugs: EPIDIOLEX should be gradually withdrawn to minimize the risk of increased seizure frequency and status epilepticus. (5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions (10% or more for EPIDIOLEX and greater than placebo) in patients with Lennox-Gastaut syndrome or Dravet syndrome are: somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; and infections. (6.1)

The most common adverse reactions (10% or more for EPIDIOLEX and greater than placebo) in patients with tuberous sclerosis complex are: diarrhea; transaminase elevations; decreased appetite; somnolence; pyrexia; and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Greenwich Biosciences at 1-833-424-6724 (1-833-GBIOSCI) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong inducer of CYP3A4 or CYP2C19: Consider dose increase of EPIDIOLEX. (7.1)
- Consider a dose reduction of substrates of UGT1A9, UGT2B7, CYP1A2, CYP2C8, CYP2C9, CYP2C19 (e.g., clobazam), and orally administered P-gp substrates. (7.2)
- A lower starting dose of orally administered everolimus is recommended. (7.2)
- Substrates of CYP2B6 may also require dose adjustment. (7.2)

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 02/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

Table 3: Adverse Reactions in Patients Treated with EPIDIOLEX in Controlled Trials of LGS and DS (Studies 1, 2, and 3)

Adverse Reactions	EPIDIOLEX		Placebo
	10 mg/kg/day	20 mg/kg/day	
	N=75 %	N=238 %	N=227 %
Hepatic Disorders			
Transaminases elevated	8	16	3
Gastrointestinal Disorders			
Decreased appetite	16	22	5
Diarrhea	9	20	9
Weight decreased	3	5	1
Gastroenteritis	0	4	1
Abdominal pain, discomfort	3	3	1
Nervous System Disorders			
Somnolence	23	25	8
Fatigue, malaise, asthenia	11	12	4
Lethargy	4	8	2
Sedation	3	6	1
Irritability, agitation	9	5	2
Aggression, anger	3	5	<1
Insomnia, sleep disorder, poor quality sleep	11	5	4
Drooling, salivary hypersecretion	1	4	<1
Gait disturbance	3	2	<1
Infections			
Infection, all	41	40	31
Infection, other	25	21	24
Infection, viral	7	11	6
Pneumonia	8	5	1
Infection, fungal	1	3	0
Other			
Rash	7	13	3
Hypoxia, respiratory failure	3	3	1

Adverse reactions were similar across LGS and DS in pediatric and adult patients.

Patients with TSC

In a placebo-controlled trial of patients with TSC (Study 4), 148 patients received EPIDIOLEX *[see Clinical Studies (14.3)]*. Adverse reactions are presented below; the duration of treatment in this trial was up to 16 weeks. Approximately 42% of patients were female, 90% were Caucasian, and the mean age was 14 years (range 1 to 57 years). All patients but one (25 mg/kg/day group) were taking other AEDs.

In the controlled trial in TSC, the rate of discontinuation as a result of any adverse reaction was 11% for patients taking EPIDIOLEX 25 mg/kg/day and 3% for patients on placebo. The most frequent cause of discontinuation was rash (5%).

The most common adverse reactions that occurred in EPIDIOLEX-treated patients with TSC (incidence at least 10% at the recommended dosage and greater than placebo) were diarrhea; transaminase elevations; decreased appetite; somnolence; pyrexia; and vomiting.

Table 4 lists the adverse reactions that were reported in at least 3% of EPIDIOLEX-treated patients, and at a rate greater than those on placebo, in the placebo-controlled trial in TSC.

Table 4: Adverse Reactions in Patients Treated with EPIDIOLEX in Controlled Trial of TSC (Study 4)

Adverse Reactions	**EPIDIOLEX 25 mg/kg/day N = 75 %**	**Placebo N = 76 %**
Hematological changes		
Anemia	7	1
Platelet count decreased	5	1
Eosinophil count increased	5	0
Hepatic Disorders		
Transaminases elevated	25	0
Gastrointestinal Disorders		
Diarrhea	31	25
Decreased appetite	20	12
Vomiting	17	9
Nausea	9	3
Gastroenteritis	8	7
Weight decreased	7	0
Nervous System Disorders		
Somnolence	13	9
Gait disturbance	9	5
Fatigue, malaise, asthenia	5	1
Infections		
Ear infection	8	3
Urinary tract infection	5	0
Pneumonia	4	1
Other		
Pyrexia	19	8
Rash	8	4
Rhinorrhea	4	0

Adverse reactions were similar in pediatric and adult patients with TSC.

Additional Adverse Reactions in Patients with LGS, DS, or TSC

Decreased Weight

EPIDIOLEX can cause weight loss. In the controlled trials of patients with LGS or DS (10 and 20 mg/kg/day), based on measured weights, 16% of EPIDIOLEX-treated patients had a decrease in weight of at least 5% from their baseline weight, compared to 8% of patients on placebo. The decrease in weight appeared to be dose-related, with 18% of patients on EPIDIOLEX 20 mg/kg/day experiencing a decrease in weight at least 5%, compared to 9% in patients on EPIDIOLEX 10 mg/kg/day. In the controlled trial of patients with TSC (25 mg/kg/day), 31% of EPIDIOLEX-treated patients had a decrease in weight of at least 5% from their baseline weight, compared to 8% of patients on placebo. In some cases, the decreased weight was reported as an adverse event (see Tables 3 and 4).

Hematologic Abnormalities

EPIDIOLEX can cause decreases in hemoglobin and hematocrit. In controlled trials of patients with LGS or DS, the mean decrease in hemoglobin from baseline to end of treatment was -0.42 g/dL in EPIDIOLEX-treated patients receiving 10 or 20 mg/kg/day and -0.03 g/dL in patients on placebo. A corresponding decrease in hematocrit was also observed, with a mean change of -1.5% in EPIDIOLEX-treated patients, and -0.4% in patients on placebo. In the trial of patients with TSC, the mean decrease in hemoglobin from baseline to end of treatment was -0.37 g/dL in EPIDIOLEX-treated patients receiving 25 mg/kg/day and 0.07 g/dL in patients on placebo. A corresponding decrease in hematocrit was also observed, with a mean change of -1.2% in EPIDIOLEX-treated patients, and -0.2% in patients on placebo.

There was no effect on red blood cell indices. Thirty percent (30%) of EPIDIOLEX-treated patients with LGS and DS and 38% of EPIDIOLEX-treated patients with TSC developed a new laboratory-defined anemia during the course of the study (defined as a normal hemoglobin concentration at baseline, with a reported value less than the lower limit of normal at a subsequent time point), versus 13% of patients with LGS and DS on placebo and 15% of patients with TSC on placebo.

Increases in Creatinine

EPIDIOLEX can cause elevations in serum creatinine. The mechanism has not yet been determined. In controlled studies in healthy adults and in patients with LGS, DS, and TSC, an increase in serum creatinine of approximately 10% was observed within 2 weeks of starting EPIDIOLEX. The increase was reversible in healthy adults. Reversibility was not assessed in studies in LGS, DS, or TSC.

Increases in Pneumonia with Concomitant Clobazam

Pneumonia has been observed in controlled trials in patients with LGS and DS more frequently with clobazam (7 of 41 [17%] in patients receiving 10 mg/kg/day EPIDIOLEX, 13 of 125 [10%] in patients receiving 20 mg/kg/day EPIDIOLEX, and 1 of 123 [1%] receiving placebo) than without concomitant clobazam (0% in patients receiving 10 mg/kg/day EPIDIOLEX, 4 of 113 [4%] in patients receiving 20 mg/kg/day EPIDIOLEX, and 1 of 104 [1%] receiving placebo). In the controlled trial in patients with TSC, pneumonia was observed more frequently with concomitant clobazam (3 of 18 [17%] in patients receiving 25 mg/kg/day EPIDIOLEX and 0 of 25 [0%] receiving placebo) than without clobazam (0 of 57 [0%] in patients receiving 25 mg/kg/day EPIDIOLEX and 1 of 51 [2%] receiving placebo).

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on EPIDIOLEX

Strong CYP3A4 or CYP2C19 Inducers

Coadministration with a strong CYP3A4 and CYP2C19 inducer (rifampin 600 mg once daily) decreased cannabidiol and 7-OH-CBD plasma concentrations by approximately 32% and 63%. The impact of such changes on efficacy of EPIDIOLEX are not known *[see Clinical Pharmacology (12.3)]*. Consider an increase in EPIDIOLEX dosage (based on clinical response and tolerability) up to 2-fold, when coadministered with a strong CYP3A4 and/or CYP2C19 inducer.

7.2 Effect of EPIDIOLEX on Other Drugs

UGT1A9, UGT2B7, CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 Substrates

Cannabidiol is a weak inhibitor of CYP1A2 *[see Clinical Pharmacology (12.3)]*. Increases in exposure of sensitive CYP1A2 substrates (e.g., caffeine, theophylline, or tizanidine) may be observed when coadministered with cannabidiol.

In vitro data predict drug-drug interactions with CYP2B6 substrates (e.g., bupropion, efavirenz), uridine 5'-diphospho-glucuronosyltransferase 1A9 (UGT1A9) substrates (e.g., diflunisal, propofol, fenofibrate), and UGT2B7 substrates (e.g., gemfibrozil, lamotrigine, morphine, lorazepam) when coadministered with EPIDIOLEX. Coadministration of EPIDIOLEX is also predicted to cause clinically significant interactions with CYP2C8 and CYP2C9 (e.g., phenytoin) substrates. Because of potential inhibition of enzyme activity, consider a reduction in dosage of substrates of UGT1A9, UGT2B7, CYP1A2, CYP2C8, and CYP2C9, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with EPIDIOLEX. Because of the potential for both induction and inhibition of enzyme activity, consider adjusting dosage of substrates of CYP2B6, as clinically appropriate.

Sensitive CYP2C19 Substrates

In vivo data show that coadministration of EPIDIOLEX increases plasma concentrations of drugs that are metabolized by (i.e., are substrates of) CYP2C19 (e.g., diazepam) and may increase the risk of adverse reactions with these substrates *[see Clinical Pharmacology (12.3)]*. Consider a reduction in dosage of sensitive CYP2C19 substrates, as clinically appropriate, when coadministered with EPIDIOLEX.

Clobazam

Coadministration of EPIDIOLEX produces a 3-fold increase in plasma concentrations of N-desmethylclobazam, the active metabolite of clobazam (a substrate of CYP2C19), with no effect on clobazam levels *[see Clinical Pharmacology (12.3)]*. The increase in N-desmethylclobazam may increase the risk of clobazam-related adverse reactions *[see Adverse Reactions (6.1) and Warnings and Precautions (5.1, 5.2)]*. Consider a reduction in dosage of clobazam if adverse reactions known to occur with clobazam are experienced when coadministered with EPIDIOLEX.

Stiripentol

Concomitant use of EPIDIOLEX and stiripentol causes an elevation in exposure to stiripentol *[see Clinical Pharmacology (12.3)]*. The mechanism of this interaction has not been determined. The clinical relevance of this effect is unknown, but patients should be monitored for stiripentol-related adverse drug reactions.

Sensitive P-gp Substrates Given Orally

Coadministration of EPIDIOLEX with orally administered everolimus, a P-gp and CYP3A4 substrate, results in an approximately 2.5-fold increase in mean C_{max} and AUC of everolimus *[see Clinical Pharmacology (12.3)]*. When initiating EPIDIOLEX in patients taking everolimus, monitor therapeutic drug levels of everolimus and adjust the dosage accordingly. When initiating everolimus in patients taking a stable dosage of EPIDIOLEX, a lower starting dose of everolimus is recommended, with therapeutic drug monitoring.

Increases in exposure of other orally administered P-gp substrates (e.g., sirolimus, tacrolimus, digoxin) may be observed on coadministration with EPIDIOLEX. Therapeutic drug monitoring and dose reduction of other P-gp substrates should be considered when given orally and concurrently with EPIDIOLEX.

7.3 Concomitant Use of EPIDIOLEX and Valproate

Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations *[see Warnings and Precautions (5.1)]*. If such elevations occur, discontinuation or reduction of EPIDIOLEX and/or concomitant valproate should be considered. Insufficient data are available to assess the risk of concomitant administration of other hepatotoxic drugs and EPIDIOLEX.

7.4 CNS Depressants and Alcohol

Concomitant use of EPIDIOLEX with other CNS depressants (including alcohol) may increase the risk of sedation and somnolence *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), such as EPIDIOLEX, during pregnancy. Encourage women who are taking EPIDIOLEX during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling the toll free number 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org/.

Risk Summary

There are no adequate data on the developmental risks associated with the use of EPIDIOLEX in pregnant women. Administration of cannabidiol to pregnant animals produced evidence of developmental toxicity (increased embryofetal mortality in rats and decreased fetal body weights in rabbits; decreased growth, delayed sexual maturation, long-term neurobehavioral changes, and adverse effects on the reproductive system in rat offspring) at maternal plasma exposures similar to (rabbit) or greater than (rat) that in humans at therapeutic doses *(see Animal Data).* In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively. The background risks of major birth defects and miscarriage for the indicated populations are unknown.

Data

Animal Data

Oral administration of cannabidiol (0, 75, 150, or 250 mg/kg/day) to pregnant rats throughout the period of organogenesis resulted in embryofetal mortality at the highest dose tested. There were no other drug-related maternal or developmental effects. The highest no-effect dose for embryofetal toxicity in rats was associated with maternal plasma cannabidiol exposures (AUC) approximately 16 and 9 times that in humans at the recommended human doses (RHD) of 20 and 25 mg/kg/day, respectively.

Oral administration of cannabidiol (0, 50, 80, or 125 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in decreased fetal body weights and increased fetal structural variations at the highest dose tested, which was also associated with maternal toxicity. Maternal plasma cannabidiol exposures at the no-effect level for embryofetal developmental toxicity in rabbits were less than that in humans at the RHDs.

When cannabidiol (75, 150, or 250 mg/kg/day) was orally administered to rats throughout pregnancy and lactation, decreased growth, delayed sexual maturation, neurobehavioral changes (decreased activity), and adverse effects on male reproductive organ development (small testes in adult offspring) and fertility were observed in the offspring at the mid and high dose. These effects occurred in the absence of maternal toxicity. The no-effect dose for pre- and post-natal developmental toxicity in rats was associated with maternal plasma cannabidiol exposures approximately 9 and 5 times that in humans at the RHDs of 20 and 25 mg/kg/day, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of cannabidiol or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EPIDIOLEX and any potential adverse effects on the breastfed infant from EPIDIOLEX or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of EPIDIOLEX for the treatment of seizures associated with LGS, DS, or TSC have been established in patients 1 year of age and older. The use of EPIDIOLEX in these indications is supported by adequate and well-controlled studies in patients 2 years of age and older with LGS and DS and in patients 1 year of age and older with TSC *[see Clinical Studies (14.1, 14.2, 14.3)]*.

Safety and effectiveness of EPIDIOLEX in pediatric patients below 1 year of age have not been established.

Juvenile Animal Data

Administration of cannabidiol (subcutaneous doses of 0 or 15 mg/kg on Postnatal Days (PNDs) 4-6 followed by oral administration of 0, 100, 150, or 250 mg/kg on PNDs 7-77) to juvenile rats for 10 weeks resulted in increased body weight, delayed male sexual maturation, neurobehavioral effects (decreased locomotor activity and auditory startle habituation), increased bone mineral density, and liver hepatocyte vacuolation. A no-effect dose was not established. The lowest dose causing developmental toxicity in juvenile rats (15 sc/100 po mg/kg) was associated with cannabidiol exposures (AUC) approximately 15 and 8 times that in humans at the RHDs of 20 and 25 mg/kg/day, respectively.

8.5 Geriatric Use

Clinical trials of EPIDIOLEX in the treatment of LGS, DS, and TSC did not include a sufficient number of patients aged above 55 years to determine whether or not they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of

concomitant disease or other drug therapy *[see Dosage and Administration (2.6), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

Because of an increase in exposure to EPIDIOLEX, dosage adjustments are necessary in patients with moderate or severe hepatic impairment *[see Dosage and Administration (2.6), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*. EPIDIOLEX does not require dosage adjustments in patients with mild hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

EPIDIOLEX is not a controlled substance.

9.2 Abuse

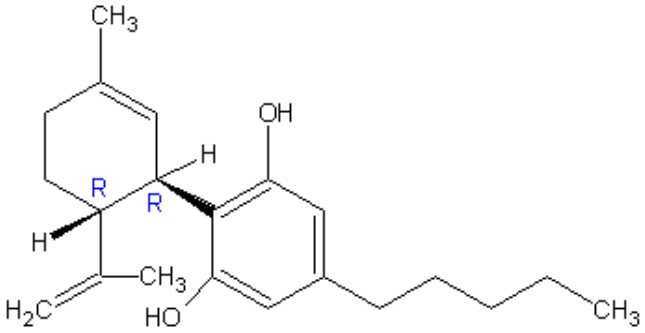
Animal abuse-related studies show that cannabidiol does not produce cannabinoid-like behavioral responses, including generalization to delta-9-tetrahydrocannabinol (THC) in a drug discrimination study. Cannabidiol also does not produce animal self-administration, suggesting it does not produce rewarding effects. In a human abuse potential study, acute administration of cannabidiol to non-dependent adult recreational drug users at therapeutic and supratherapeutic doses of 750, 1500, and 4500 mg in the fasted state (equivalent respectively to 10, 20, and 60 mg/kg in a 75 kg adult) produced responses on positive subjective measures such as Drug Liking and Take Drug Again that were within the acceptable placebo range. In contrast, 10 and 30 mg of dronabinol (synthetic THC) and 2 mg alprazolam produced large increases on positive subjective measures compared to placebo that were statistically significantly greater than those produced by cannabidiol. In other Phase 1 clinical studies conducted with cannabidiol, there were no reports of abuse-related adverse events.

9.3 Dependence

In a human physical dependence study, administration of cannabidiol 1500 mg/day (750 mg twice daily) to adults for 28 days did not produce signs or symptoms of withdrawal over a 6-week assessment period beginning three days after drug discontinuation. This suggests that cannabidiol likely does not produce physical dependence.

11 DESCRIPTION

Cannabidiol is a cannabinoid designated chemically as 2-[(1R,6R)-3-Methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol (IUPAC/CAS). Its empirical formula is $C_{21}H_{30}O_2$ and its molecular weight is 314.46. The chemical structure is:



Cannabidiol, the active ingredient in EPIDIOLEX, is a cannabinoid that naturally occurs in the *Cannabis sativa* L. plant.

Cannabidiol is a white to pale yellow crystalline solid. It is insoluble in water and is soluble in organic solvents.

EPIDIOLEX (cannabidiol) oral solution is a clear, colorless to yellow liquid containing cannabidiol at a concentration of 100 mg/mL. Inactive ingredients include dehydrated alcohol (7.9% w/v), sesame seed oil, strawberry flavor, and sucralose. EPIDIOLEX contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanisms by which EPIDIOLEX exerts its anticonvulsant effect in humans are unknown. Cannabidiol does not appear to exert its anticonvulsant effects through interaction with cannabinoid receptors.

12.2 Pharmacodynamics

There are no relevant data on the pharmacodynamic effects of cannabidiol.

12.3 Pharmacokinetics

Cannabidiol demonstrated an increase in exposure that was less than dose-proportional over the range of 5 to 25 mg/kg/day in patients.

Absorption

Cannabidiol has a time to maximum plasma concentration (T_{max}) of 2.5 to 5 hours at steady state (C_{ss}).

Effect of Food

Coadministration of EPIDIOLEX (750 or 1500 mg) with a high-fat/high-calorie meal increased C_{max} by 5-fold, AUC by 4-fold, and reduced the total variability, compared with the fasted state in healthy volunteers *[see Dosage and Administration (2.4)]*. Coadministration of EPIDIOLEX with a low-fat/low-calorie meal increased C_{max} and AUC by 4-fold and 3-fold, respectively. Furthermore, coadministration of EPIDIOLEX with bovine milk increased exposure by approximately 3-fold for C_{max} and 2.5-fold for AUC.

Coadministration of EPIDIOLEX with alcohol also caused increased exposure to cannabidiol, with 93% increased C_{max} and 63% greater AUC.

Distribution

The apparent volume of distribution in healthy volunteers was 20963 L to 42849 L. Protein binding of the cannabidiol and its metabolites was > 94% in vitro.

Elimination

The half-life of cannabidiol in plasma was 56 to 61 hours after twice-daily dosing for 7 days in healthy volunteers. The plasma clearance of cannabidiol following a single EPIDIOLEX 1500 mg dose (approximately equal to the 20 mg/kg/day dosage) is 1111 L/h.

Metabolism

Cannabidiol is metabolized in the liver and the gut (primarily in the liver) by CYP2C19 and CYP3A4 enzymes, and UGT1A7, UGT1A9, and UGT2B7 isoforms.

After repeat dosing, the active metabolite of cannabidiol, 7-OH-CBD, has a 38% lower AUC than the parent drug. The 7-OH-CBD metabolite is converted to 7-COOH-CBD, which has an approximately 40-fold higher AUC than the parent drug. Based on preclinical models of seizure, the 7-OH-CBD metabolite is active; however, the 7-COOH-CBD metabolite is not active.

Excretion

EPIDIOLEX is excreted in feces, with minor renal clearance.

Specific Populations

Patients with Hepatic Impairment

No effects on the exposures of cannabidiol or metabolite exposures were observed following administration of a single dose of EPIDIOLEX 200 mg in patients with mild (Child-Pugh A) hepatic impairment. Patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment had an approximately 2.5 to 5.2-fold higher AUC, compared with healthy volunteers with normal hepatic function *[see Dosage and Administration (2.6), Warnings and Precautions (5.1), Use in Specific Populations (8.6)]*.

Drug Interaction Studies

In Vitro Assessment of Drug Interactions

Drug Metabolizing Enzymes *[see Drug Interactions (7.1, 7.2)]*

Cannabidiol is a substrate for CYP3A4 and CYP2C19. Cannabidiol has the potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 at clinically relevant concentrations.

Cannabidiol may induce or inhibit CYP2B6 at clinically relevant concentrations.

Cannabidiol inhibits uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes UGT1A9 and UGT2B7, but does not inhibit the UGT1A1, UGT1A3, UGT1A4, UGT1A6, or UGT2B17 isoforms.

Transporters

Cannabidiol and the cannabidiol metabolite, 7-OH-CBD, are not anticipated to interact with BCRP, BSEP, MDR1/P-gp, OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K, OATP1B1, or OATP1B3. However, due to limitations of the *in vitro* testing procedure, inhibition of P-gp mediated efflux by cannabidiol in the intestine could not be excluded. *In vivo* data show that CBD can affect P-gp efflux activity in the intestine *[see In Vivo Assessment of Drug Interactions]*.

The cannabidiol metabolite, 7-COOH-CBD, is not a substrate of BCRP, OATP1B1, OATP1B3, or OCT1. However, 7-COOH-CBD is a substrate for P-gp. 7-COOH-CBD is an inhibitor of transport mediated via BCRP and BSEP at clinically relevant concentrations.

In Vivo Assessment of Drug Interactions

Drug Interaction Studies with AEDs

Clobazam and Valproate

The interaction potential with other AEDs (clobazam and valproate) was evaluated in dedicated clinical studies following coadministration of EPIDIOLEX (750 mg twice daily in healthy volunteers and 20 mg/kg/day in patients).

Coadministration with clobazam in healthy volunteers increased the cannabidiol active metabolite 7-OH-CBD mean C_{max} by 73% and AUC by 47%; and increased the clobazam active metabolite, N-desmethylclobazam, C_{max} and AUC by approximately 3-fold, with no effect on clobazam levels *[see Drug Interactions (7.2)]*.

When EPIDIOLEX was coadministered with valproate in a healthy-volunteer trial, there was no effect on the systemic exposure to valproate. In a separate study in epilepsy patients investigating the effect of EPIDIOLEX on valproate exposure, there were decreases in both the plasma C_{max} and AUC of valproate, which were not clinically relevant (approximately 17% and 21%, respectively), and a decrease in exposure of the putative hepatotoxic metabolite of valproate, 2-propyl-4-pentenoic acid (approximately 28% and 33%, respectively).

In the healthy-volunteer trial, coadministration with valproate resulted in no clinically relevant changes in exposure to cannabidiol or its major metabolites (cannabidiol C_{max} decreased by 26%; 6-OH-CBD AUC increased by 27%; 7-OH-CBD AUC increased by 22%; 7-COOH-CBD C_{max} and AUC increased by 25% and 32%, respectively).

Effect of EPIDIOLEX on Midazolam

Coadministration of EPIDIOLEX with midazolam (a sensitive CYP3A4 substrate) did not result in changes in plasma concentrations of midazolam compared to midazolam administered alone.